In claim 10, lines 6, 17, 20, 22, 26, 30, 32, 37, 40, 48, 49 delete "reference" (i.e., all occurrences)

In claim 29, line 5, replace "reference" with --first--.

In claim 35, lines 6, 16, 19, 21, 24, 26, 29, 33, 42, 43, delete "reference", and para (c), line 2, replace "reference" with --first--.

In claim 46, lines 16, 27, 30, 32, 36, 40, 42, 47, 58, 59, delete "reference", and para (c), line 2, replace "reference" with --first--.

In claims 26 and 34 delete "reference" (all occurrences).

In claims 30-32 replace "a reference" with --the first--.

In claim 33, replace "reference amino acid sequence" with --first vertebrate growth hormone--.

In claim 38, replace "reference" (all occurrences) with --first--.

In claim 64, lines 5, 15, 19, 22, 24, 28, 29, 31, 35, 37, 44, 45, delete "reference".

Please rewrite claim 63 as follows:

63 (amended). [The] A method [of claim 46] of reducing growth hormone activity in a mammalian subject which comprises administering to the subject a DNA molecule comprising a coding sequence encoding a mammalian growth hormone receptor antagonist which is a polypeptide, under conditions conducive to the integration of said DNA into the genome of one or more cells of said subject, said subject subsequently expressing a growth hormone activity-antagonizing and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth hormone antagonist activity in said subject,

where said polypeptide comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino

acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first vertebrate growth hormone's receptor of a single substitution mutant of the first vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said first vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue

E4

E4

furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first vertebrate growth hormone but deleted in a second vertebrate growth hormone

whereby the growth hormone activity in said subject is reduced, in which the subject is human.

In claims 19-24, insert --, if any,-- after "non-conservative substitution".

Please add the following new claims:

75. The DNA molecule of claim 11 wherein the amino acid of (I) is arginine.

76. The DNA molecule of claim 11 wherein the amino acid of (I) is tryptophan.

77. The DNA molecule of claim 11 wherein the amino acid of (I) is proline.

78. The DNA molecule of claim 11 wherein the amino acid of (I) is lysine.

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79. The DNA molecule of claim 11 wherein the amino acid of (I) is leucine.

80. The DNA molecule of claim 11 wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is substituted with an amino acid at least as large as leucine.

81. A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a mutant polypeptide comprising an amino acid sequence, said polypeptide being a mutant of a vertebrate growth hormone, the amino acid sequence of said mutant of a vertebrate growth hormone comprising a substitution of the glycine of said vertebrate growth hormone corresponding to Gly119 of bovine growth hormone, with an amino acid other than glycine or alanine,

said polypeptide having growth hormone receptor antagonist

activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

82. The DNA molecule of claim 81 where said amino acid sequence comprises an alpha helix which is at least 50% identical to the third alpha helix of bovine or human growth hormone.

83. The DNA molecule of claim 81 where said amino acid sequence comprises an alpha helix which is at least 80% identical to the third alpha helix of bovine or human growth hormone.

84. The DNA molecule of claim 81 where said amino acid sequence is at least 50% identical with the amino acid sequence of bovine or human growth hormone.

85. The DNA molecule of claim 81 where said amino acid sequence is at least 80% identical with the amino acid sequence of bovine or human growth hormone.

86. The DNA molecule of claim 81 where the amino acid sequence of said mutant of said vertebrate growth hormone further comprises at least one substitution of another amino acid in said vertebrate growth hormone, where said another amino acid corresponds to an amino acid of bovine or human growth hormone which is not conserved among the vertebrate growth hormones.

87. The DNA molecule of claim 86 where said substitution of another amino acid is with an amino acid found at that site in a different vertebrate growth hormone.

88. A method of reducing growth hormone activity in a mammalian subject which comprises administering to the subject a DNA molecule comprising a coding sequence encoding a mammalian growth hormone receptor antagonist which is a polypeptide, under conditions conducive to the integration of said DNA into the genome of one or more cells of said subject, said subject subsequently expressing a growth hormone activity-antagonizing

and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth hormone antagonist activity in said subject,

where said polypeptide is a mutant polypeptide comprising an amino acid sequence, said polypeptide being a mutant of a vertebrate growth hormone, the amino acid sequence of said mutant of a vertebrate growth hormone comprising a substitution of the glycine of said vertebrate growth hormone corresponding to Gly119 of bovine growth hormone, with an amino acid other than glycine or alanine,

said polypeptide having mammalian growth hormone receptor antagonist activity,

whereby the growth hormone activity in said subject is reduced.

89. The method of claim 81 wherein the mammal suffers from an excessive growth rate.

90. The method of claim 89 in which the mammal suffers from gigantism.

91. The method of claim 89 in which the mammal suffers from acromegaly.

92. The method of claim 88 wherein the mammal suffers from diabetes.

93. The method of claim 88 in which the mammal suffers from diabetic retinopathy.

94. The method of claim 88 in which the mammal suffers from glomerulosclerosis.

95. The method of claim 88 in which the mammal suffers from hypercholesterolemia.

96. The method of claim 88 wherein the mammal suffers from a tumor whose growth is stimulated by endogenous growth hormone.

97. The method of claim 88 in which the mammal suffers from a tumor which secretes growth hormone.

98. The method of claim 96 in which the mammal suffers from a tumor whose growth is stimulated by autocrine secretions of

growth hormone.

99. The DNA molecule of claim 10 where in said polypeptide the amino acid corresponding to Gly-119 of bovine growth hormone is not proline.

100. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with arginine.

101. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with lysine.

102. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with tryptophan.

103. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with leucine.

104. The DNA molecule of claim 81 where said substitution corresponding to Gly 119 is with proline.

105. The DNA molecule of claim 81 where the amino acid sequence of said mutant further comprises at least one other substitution of an amino acid of said vertebrate growth hormone said other substitution being at a position outside the third alpha helix thereof.

106. The DNA molecule of claim 81 where said amino acid sequence comprises an alpha helix which is at least 50% identical to the third alpha helix of a vertebrate growth hormone.--

Please rewrite claim 39 as follows:

39 (amended). The DNA molecule of claim 38 wherein <u>said first vertebrate growth hormone is bovine growth hormone and</u> said helix corresponds to the third alpha helix of [bovine] <u>said first vertebrate</u> growth hormone.

<u>REMARKS</u>

<u>1. General Matters</u>

In the papers filed November 8, 1999, Applicants requested an interview "prior to the next action on this case".

In §1 of the office action mailed January 31, 2000,